Reconsideration of the application is respectfully requested.

## I. AMENDMENT

**In the Claims**

Please amend the claims as follows:

1. (Twice Amended) A composition comprising a first polynucleotide that hybridizes to a second, Bcl-2-encoding polynucleotide under intracellular conditions and a neutral lipid associated with said first polynucleotide[, and wherein said composition contains no cationic lipid].

9. (Twice Amended) A composition comprising an expression construct that encodes a first polynucleotide that hybridizes to a second, Bcl-2-encoding polynucleotide under intracellular conditions, wherein said [first polynucleotide] construct is under the control of a promoter that is active in eukaryotic cells[,] and [wherein said construct is] associated with a neutral lipid[, and further wherein said composition contains no cationic lipid].

10. (Twice Amended) A method of inhibiting proliferation of a Bcl-2-associated disease cell comprising obtaining a first polynucleotide that hybridizes to a second[, Bcl-2-encoding] polynucleotide under intracellular conditions, mixing the first polynucleotide with a neutral lipid to form a composition comprising a polynucleotide/lipid association, and administering said association to said Bcl-2-associated disease cell to inhibit the proliferation of said disease cell, wherein said cell [expresses both Bcl-2 and Bax] has a t(14;18) translocation, and wherein the second polynucleotide comprises at least 8 bases of the translation initiation site of Bcl-2 mRNA.

Please add claims 21-37, as follows:

--21. A method of inhibiting proliferation of a Bcl-2-associated disease cell having a t(14;18) translocation comprising:

(a) obtaining an oligonucleotide nucleotide of from about 8 to about 50 bases and complementary to at least 8 consecutive bases of the translation initiation site of Bcl-2 mRNA;

(b) mixing the oligonucleotide with a neutral lipid to form a neutral oligonucleotide/lipid association; and

(c) administering said association to said Bcl-2-associated disease cell to inhibit the proliferation of said disease cell.

22. The method of claim 21, wherein the cell is a cancer cell.

23. The method of claim 22, wherein said cancer cell is a follicular lymphoma cell.

24. The method of claim 21, comprising a liposome formed from the lipid.

25. The method of claim 24, wherein the liposome encapsulates the polynucleotide.

26. The method of claim 21, wherein said administering takes place in an animal.

27. The method of claim 26, wherein said animal is a human.

28. The method of claim 27, wherein said composition is delivered to said human in a volume of 0.50-10.0 ml per dose.

29. The method of claim 27, wherein said composition is delivered to said human in an amount of from about 5 to about 30 mg polynucleotide per $m^2$.

30. The method of claim 29, wherein said composition is administered three times per week for eight weeks.

31. A neutral lipid oligonucleotide association comprising a neutral lipid associated with an oligonucleotide of from about 8 to about 50 bases and complementary to at least 8 bases of the translation initiation site of Bcl-2 mRNA.

32. The neutral lipid oligonucleotide association of claim 31, wherein the oligonucleotide has the sequence CAGCGTGGGCCATCCTTC (SEQ ID NO:1).

33. The neutral lipid oligonucleotide association of claim 31, comprising a liposome formed from the lipid.

34. The neutral lipid oligonucleotide association of claim 33, wherein the oligonucleotide is encapsulated in the liposome.

35. The neutral lipid oligonucleotide association of claim 31, wherein the lipid is a phosphatidylcholine, a phosphatidylglycerol, or a phosphatidylethanolamine.

36. The neutral lipid oligonucleotide association of claim 35, wherein the lipid is dioleoylphosphatidylcholine.

37. A composition comprising a neutral lipid associated with an expression construct that encodes an oligonucleotide of from about 8 to about 50 bases and complementary to at least 8 bases of the translation initiation site of Bcl-2 mRNA, wherein the construct is under the control of a promoter that is active in eukaryotic cells.--

**In the specification**

Please amend the specification as follows:

At p. 6, line 2, after "lipid" please delete "a comprising".

At p. 37, line 14, please delete "mmol" and insert "μmol" therefor.

At p. 37, line 17, please delete "mmol" and insert "μmol" therefor.

At p. 37, line 23, please delete "mmol" and insert "μmol" therefor.

## II. RESPONSE TO OFFICE ACTION

### A. State of the Claims

Claims 1-20 were considered in the Action. Claims 1, 9 and 10 have been amended. Claims 21-37 have been added. Therefore, claims 1-37 are currently pending.

Claims 1 and 9 were amended to exclude the negative limitation added in the last response in response to the new matter rejection and to clarify the nature of the invention as

being drawn to compositions of lipid associations containing neutral lipids but not necessarily excluding cationic lipids. Claim 9 was also amended to clarify that it is the construct and not the encoded oligonucleotide that is under the control of the promoter.

Claim 10 was amended in response to an indefiniteness rejection and to more distinctly clarify the nature of the invention as being directed to administering the claimed polynucleotide/lipid association to a disease cell so as to inhibit its proliferation and to clarify that the second Bcl-2 encoding polynucleotide should contain at least 8 bases which encode for the translation initiation site of Bcl-2 mRNA. It is Applicants' position that the disclosed method is not limited to the treatment of only Bcl-2 associated diseases having a t(14;18) translocation. However, to expedite prosecution, Applicants have amended claim 10 in accordance with the Examiner's suggestion without prejudice to further prosecute method claims not limited to such Bcl-2 associated diseases in subsequent applications. Support for this amendment is found at page 5, line 27 to page 6, line 6 and page 10, line 25 to page 14, line 7.

Claims 21-30 were added to cover methods of prohibiting the proliferation of disease cells having t(14;18) translocations. Support for these claims may be found in the specification at, for example, p. 34, lines 3-11, p. 38, lines 14-16, page 5, line 27 to page 6, line 6 and page 10, line 25 to page 14, line 7, as well as the claims as originally filed.

Claims 31-37 were added to clarify the nature of some of the lipid-associated antisense oligonucleotide compositions. These claims are supported by the specification at, for example, page 4, line 15 to page 6, line 15 and page 10, line 24 to page 21, line 11.

The specification was amended to correct some minor typographical errors. Support for these amendments may be found in the specification at, for example, p. 8, lines 5-18, p. 8, line 24 to p. 9, line 3, and FIGS. 4A, 4B and 6A.

**B. The Rejection of Claims 1-9 under 35 U.S.C. §112, First Paragraph, Has Been Overcome.**

The Action initially rejected Claims 1-9 under 35 U.S.C. 112, first paragraph, for containing new matter. Specifically, the Action stated that the negative limitation excluding cationic lipids from the polynucleotide/lipid composition which was added in the last response was not be supported by the initial disclosure. To facilitate prosecution and because Applicants do not believe that this limitation is necessary to distinguish and define the present invention, Applicants have amended claims 1 and 9 to exclude any reference to this negative limitation. Therefore, Applicants respectfully request that this rejection be withdrawn.

**C. Claims 10-20 Are Enabled.**

The Action next rejected claims 10-20 as lacking enablement for not teaching how to use the claimed methods. Initially, the Action argues that the specification does not enable the treatment of all BCL-2 associated diseases, including diseases where cells overexpress BCL-2 for reasons other than a t(14;18) translocation whether or not these cells express Bax, and asserts that the use of immunocompromised mice in *in vivo* experiments is completely unpredictive of results in normal patients. The Action also argues that the breadth of polynucleotides covered, which encompass any polynucleotide that hybridizes to a BCL-2 polynucleotide, is not enabled.

It is also argued that the use of lipids other than neutral phospholipids are not enabled. Claims 18-20 drawn to administration to a human are further rejected. Applicants respectfully traverse.

**1. Claims 10-17 are objectively enabled.**

Enablement is a legal determination of whether a patent enables one skilled in the art to make and use the claimed invention. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986). The enablement requirement for patent validity is met if the description enables any mode of making and using the claimed invention. *Engel Industries, Inc. v. Lockformer Co.*, 946 F.2d 1528, 1533 (Fed. Cir. 1991).

Applicants submit that contrary to the Action's position, the specification more than adequately describes how to make and use the claimed invention. The specification describes the use of liposomal antisense Bcl-2 in cells that overexpress Bcl-2. In Johnson cells used as a model in the present disclosure, overexpression is due to a t(14;18) translocation as described in the specification at page 34. At page 38, the specification again states that the inhibition of cell growth was seen in those cells with the t(14;18) translocation, and not in those cells that do not have the translocation and do not overexpress Bcl-2. In addition, the specification at page 37 describes the role of the Bcl-2/Bax ratio in the induction of apoptosis. Therefore the present specification does describe how to use the present invention, by choosing cell lines that overexpress Bcl-2 and that also express Bax.

It is well established that a rejection based on a lack of enablement must be supported. For example, the Court in *Gould v. Mossinghoff*, 229 U.S.P.Q. 1, 13-14 (D.D.C. 1985) stated:

> In examining a patent application, the PTO is required to assume that the specification complies with the enablement provisions of Section 112 unless it has "acceptable evidence or reasoning" to suggest otherwise. *In re Marzocchi*, 439 F.2d 220, 223-24, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971).

> The PTO thus must provide reasons supported by the record as a whole what the specification is not enabling. *Application of Angstadt*, 537 F.2d 498, 504, 190 U.S.P.Q. 214, 219-220 (C.C.P.A. 1979). Then and only then does the burden shift to the applicant to show that one of ordinary skill in the art could have practiced the claimed invention without undue experimentation. *In re Strahilevitz*, 668 F.2d. 1229, 1232, 212 U.S.P.Q. 561, 563-64 (C.C.P.A. 1982). [Emphasis added.]

The Action erroneously places the burden of proof on the Applicants without offering any evidence or reasoning based on the record as a whole why the disclosure is not enabling for the pending claims. If the rejections are to be maintained, the Action's positions must be supported by citing published references or by an Examiner's Affidavit sufficient to support the rejections, as required by MPEP 2144.03. The Action's only response to the replete teachings of the specification is the assertion that the specification is not enabling because of the lack of predictability in the art of antisense technology and the lack of working examples drawn to all possible claimed embodiments. This is not sufficient to support this enablement rejection in view of the specification.

Following that logic, generic claim terms would never be enabled unless all possible species encompassed by that term were explicitly shown to be operative, contrary to well-established case law. *See In re Marzocchi*, 439 F.2d 220, 224 (C.C.P.A. 1971). *See also Chiron Corp. v. Abbott Lab.*, 1996 WL 209717, at *6 (N.D.Cal. 1996) ("[G]eneric claims are permissible so long as they meet the enablement requirement."). Although patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art, in order to satisfy the enablement requirement for patentability, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill in the relevant art how to make and use the invention as broadly as it is claimed. *In re Vaeck*, 947 F.2d 488, 496

(Fed. Cir. 1991). Satisfaction of the enablement requirement is not precluded by the necessity of some experimentation. The requirement is not satisfied, however, where "undue experimentation" is needed. *Atlas Powder Co. v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984).

Furthermore, no rationale is given as to why one of skill in the art could not readily identify inoperative polynucleotide/lipid associations employing the methods disclosed in the present invention. *See, e.g.*, Examples 3 and 4. Even if some of the claimed combinations are inoperative, the claims are not necessarily invalid. "It is not a function of the claims to specifically exclude ... possible inoperative substances." *Atlas Powder Co. v. E.I. Du Pont de Nemours*, 750 F.2d 1569, 1576-77 (Fed. Cir. 1984). "[A] patentee need not test all the embodiments of his invention." *Chiron Corp.*, 1996 WL 209717, at *6.

The Examiner has failed to meet his burden with respect to this enablement rejection. "There is no requirement in 35 U.S.C. §112 or anywhere else in the patent law that a specification convince persons skilled in the art that the assertions in the specification are correct." *Gould*, 229 U.S.P.Q. at 13 (citations omitted).

> A specification disclosure that contains a teaching of the manner and process of making and using the invention in terms that correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of 35 U.S.C. §112 unless there is reason to doubt the objective truth of the statements contained therein that must be relied on for enabling support. Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis. In any event, it is incumbent on the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning that is inconsistent with the contested statement.

*In re Marzocchi*, 439 F.2d at 223-24, (emphasis added). The Examiner has given no reasoning or support in the form of an Examiner's affidavit or cited publications to doubt the accuracy of the statements in the specification with regard to the ability of antisense BCL-2 oligonucleotide/lipid associations to inhibit the proliferation of a BCL-2 associated disease cell or to support the contention that one of skill in the art would find it unduly burdensome to practice the claimed methods in light of that disclosure.

To facilitate prosecution, Applicants have amended claim 10 to clarify the nature of the the antisense polynucleotides employed with the present invention. Applicants also point out that claims 10-20 are presently limited to polynucleotides associations with neutral lipids. Therefore, Applicants are puzzled by the enablement rejection regarding the use of lipids other than neutral lipids.

**2. The specification also enables the treatment of humans.**

The Action next asserts that the specification is not enabling for the treatment of humans (claims 18-20) in that the SCID mouse model is asserted to not be a reliable predictor for the therapeutic treatment of humans. Applicants respectfully traverse.

Applicants maintain that the mouse model is a reliable predictor of *in vivo* efficacy in treating humans afflicted with the various cancers. The Action provides insufficient support for this enablement rejection. The Action provides no references questioning the use of a mouse model, including immunocompromised mice, in the treatment of Bcl-2-associated or other diseases. Applicants request that if this rejection is to be maintained that the Examiner provide

support sufficient with respect to this proposition by citing published references or by an Examiner's Affidavit, as required by MPEP 2144.03.

Applicants also maintain that there are sufficient teachings of the efficacy of the mouse model in the instant situation. *See* Declaration of Dr. Richard Ford (attached as Exhibit A). Examples 4-6 provide protocols for *in vivo* testing, such as tests using mouse models, clinical trials and human treatment. Further, with regard to the Examiner's position that the nude mouse model is not predictive of results of normal patients, Applicants contend that the nude mouse has been used in experimental and clinical research since it was first described in 1969 (Rygaard and Povlsen, 1969), attached as Exhibit 2 to the Declaration of Dr. Richard Ford. It is generally accepted that the nude mouse model is the best indication of what can be expected from human trials as supported by numerous studies finding that transplants of human tumors into the nude mouse provide an accepted model for testing the clinical efficacy of anticancer agents (Inoue *et al.*, 1983; attached as Exhibit 3, Guiliani *et al.*, 1981; attached as Exhibit 4, Giovanella *et al.*, 1983; attached as Exhibit 5, Tashiro *et al.*, 1989, attached as Exhibit 6; Khleif and Curt in *Cancer Medicine,* 4th Ed., pp. 855-68, 1997, attached as Exhibit 8). These studies demonstrate that the mouse model emulates the clinical situation in a number of diseases and cancers including lung, breast, and ovarian cancers. Furthermore, predictions from the nude mouse model studies also correlate well with clinical studies.

The nude mouse model has also been used to screen for, study and confirm anticancer effects of numerous agents. For example, doses of compounds used in preclinical animal studies can often be correlated to studies in human clinical trials (Tashiro *et al.*, 1989, attached as Exhibit 6). Additionally, correlation between the nude mouse and human clinical responses to

cyclophosphamide, 1-(4-amino-2-methylpyrimidin-5-yl)-methyl-3-(2-chloroethyl)-3-nitrosurea hydrochloride, vinblastine and 5 fluorouracil have been shown. Other studies have employed BALB/c nude mouse model for evaluating the antitumor activity for human breast cancer treatment of a variety of drugs, including vincristine, vinblastine vindesine, dauonomycin, mitoxantrone, and 5 fluorouracil amongst others (Inoue *et al.*, 1983, attached as Exhibit 3). These studies showed good correlation between the anticancer activity of various drugs in the nude mouse model for human breast cancer and in clinical treatment in humans.

In yet another comprehensive study (Guiliani *et al.*, 1981, attached as Exhibit 4), BALB/c nude mice were transplanted with breast, colon, lung, melanoma, ovarian prostate and larynx cancers and the effects of doxorubicin on these cancer models was studied. It was found that in each case the results from the model studies correlated extremely well with clinical data. The National Cancer Institute has even employed a development scheme in assaying for *in vivo* antitumor activity in which the human tumor cell line most sensitive to an active candidate *in vitro* is tested as a xenograft in a subcutaneous implant site in a nude mouse (*Cancer: Principles & Practice of Oncology,* 5th Ed., 1997, pp. 392-94, attached as Exhibit 7). The use of severe combined immunodeficiency (SCID) mice allows for transplantation of normal and malignant hematological cells (Flavell, 1996, attached as Exhibit 9). The SCID mouse model has also been employed in the art to predict therapeutic benefits of antisense therapy in SCID mice bearing human leukemias and lymphomas (Flavell, 1996, attached as Exhibit 9).

In view of the foregoing, Applicants respectfully request that these rejections be withdrawn.

**D. The Rejection of Claims 10-20 for Indefiniteness Has Been Overcome.**

The Action rejected claims 10-20 based on 35 U.S.C. 112, second paragraph, for being indefinite for not providing a positive process step in claim 10 which clearly relates back to the preamble. Applicants have amended claim 10 to clarify that the polynucleotide/lipid association is administered to the disease cell so as to inhibit its proliferation. Applicants submit that in light of this amendment one of skill in the art would be apprised of the scope of claim 10 and therefore request that this rejection be withdrawn.

**E. Claims 1-9 Are Not Obvious Based on Evan or Reed or Green *et al.* in View of Tari *et al.***

The Action finally rejects claims 1-9 as being obvious over Evan or Reed or Green *et al.* in view of a patent to Tari *et al.* (U.S. Patent No. 5,417,978). Evans, Reed and Green are purported to teach the use of an antisense oligonucleotide targeted to BCL-2, which is preferably delivered into cells employing liposomes. The Action admits that none of these references teach a liposome made of neutral lipids, such as phosphatidylcholine, phosphatidylglycerol, phosphatidylethanolamine or dioleoylphosphatidylcholine. However, the Action argues that Tari *et al.* teaches compositions containing an antisense oligonucleotide encapsulated in a liposome employing neutral lipids, such as phosphatidylcholine or phosphatidylserine. Applicants respectfully traverse.

Applicants initially contend that the evidence of surprising and unexpected advantages associated with the use of antisense BCL-2 oligonucleotides associated with neutral lipids rebuts

any asserted *prima facie* case of obviousness. *See* Declaration of Drs. Tari and Lopez-Berestein (attached as Exhibit B).

> One way for a patent applicant to rebut a *prima facie* case of obviousness is to make a showing of "unexpected results," *i.e.*, to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected [because] that which would have been surprising would not have been obvious. The principle applies most often to predictable fields, such as chemistry, where minor changes in a product or process may yield substantially different results.

*In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995).

This evidence includes the surprising and unexpected finding that neutral lipid associations selectively inhibit cell growth as only lipid:BCL-2 antisense oligonucleotide associations, and not lipid:BCL-2 control oligonucleotide associations, induce cell growth inhibition and decreased cell viability relative to untreated cells. For example, Drs. Tari and Lopez-Berestein describe studies examining the effects of net lipid charge on antisense delivery and activity. In this study, 30 mole percent of a negatively-charged lipid (DMPG) or a positively-charged lipid (DC-CHOL) were added into lipid:BCL-2 antisense or lipid:BCL-2 control oligonucleotide associations containing a neutral lipid (70 mole percent, DOPC) and the cell growth and viability observed with these charged lipid associations were compared with that observed with lipid:BCL-2 antisense and control oligonucleotide associations containing only a neutral lipid.

Surprisingly, it was found that both the negatively- and positively-charged lipid:oligonucleotide associations were very toxic to cells, with toxicity seen aat concentrations as low as 2 μM, and non-specifically inhibited growth and decreased cell viability. For example, there was no significant difference between the viability of cells exposed to the DOPC:DMPG or

DOPC:DC-CHOL lipid:BCL-2 antisense oligonucleotide associations and the corresponding DOPC:DMPG or DOPC:DC-CHOL lipid:BCL-2 control oligonucleotide associations whereas only the cells exposed to DOPC lipid:antisense oligonucleotide associations, and not the DOPC lipid:control oligonucleotide associations, exhibited decreased viability in relation to the viability of untreated cells.

These results are surprising and unexpected as this indicates that only the neutral DOPC lipids and not charged lipids can be used to safely and effectively deliver antisense oligonucleotides to cells and thereby achieve selective cytotoxicity and cell growth inhibition. In view of the above-described studies and those disclosed in the specification, it is clear that the methods and compositions employing antisense BCL-2 in association with neutral lipids as disclosed and claimed in this application have surprising and unexpected properties with respect to similar methods and compositions employing antisense BCL-2 lipid associations wherein the lipid association has an overall positive or negative charge.

Applicants also contend that the cited references also contain no suggestion or motivation to make the appropriate combination. It is well settled in patent law that "obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art." MPEP § 2143.01; *see also In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 351 (Fed. Cir. 1992).

Furthermore, the fact that a reference or references can be combined or modified is not sufficient to establish obviousness. The mere fact that combination or modification of a

reference or references is possible does not establish obviousness of the resultant combination unless the prior art also suggests the desirability of the combination, *i.e.*, unless the prior art provides motivation to produce the resultant combination. *In re Mills*, 916 F.2d 680, 682 (Fed. Cir. 1990); *see also* MPEP § 2143.01, page 2100-91.

Applicants therefore respectfully request that this rejection be withdrawn.

**F. Conclusions**

Applicants have submitted remarks which are believed to place the present claims in condition for allowance. In view of this, Applicants respectfully request that the present claims be passed for allowance. Should the Examiner have any comments or questions with regard to any statements contained herein, or any suggestions as to claim modification, the Examiner is respectfully requested to contact the Applicants' representative listed below at (512) 418-3055.

Please date-stamp and return the enclosed postcard evidencing receipt of these materials.

Respectfully submitted,

David L. Parker
Reg. No. 32,165
Attorney for Applicants

ARNOLD, WHITE & DURKEE
P.O. Box 4433
Houston, Texas 77210-4433
(512) 418-3000

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